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Abstract: The first enantioselective total synthesis of the complex tricarbocyclic sesquiterpenoid periconianone A based on a postulated biogenesis is reported. Key elements of the synthetic route include the use of an isopropenyl group as a removable directing group for stereoselective synthesis, a sequence featuring a Rh-mediated O–H insertion/[3,3]-sigmatropic rearrangement and subsequent -ketol rearrangement, and a late stage aldol reaction to furnish the complex cage-like framework.

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Total Synthesis of the Sesquiterpenoid Periconianone A Based on a Postulated Biogenesis

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Supporting Information Placeholder

ABSTRACT: *The first enantioselective total synthesis of the complex tricarbocyclic sesquiterpenoid periconianone A based on a postulated biogenesis is reported. Key elements of the synthetic route include the use of an isopropenyl group as a removable directing group for stereoselective synthesis, a sequence featuring a Rh-mediated O-H insertion/[3,3]-sigmatropic rearrangement and subsequent α-ketol rearrangement, and a late stage aldol reaction to furnish the complex cage-like framework.*

The architectural complexity of terpenes has fascinated scientists for centuries, and the challenges associated with their intricate structure have fueled innovation in scientific fields from synthetic methodology to enzymology.[1] Structural diversity in terpene biosynthesis is usually achieved at the initial cyclase phase by both polyene cyclizations and cationic rearrangements.[2] In contrast, the cage-like and rigid carbocyclic 6/6/6 framework of periconianone A (**1**), isolated from the endophytic fungus *Periconia* sp., is biosynthetically proposed to be the result of an unusual late-stage aldol cyclization of the highly oxidized bicyclic eremophilane precursor **A** (Figure 1).[3] Such a C4-C12 linkage is to our knowledge unprecedented in other sesquiterpenoids and its construction involves formation of a motif with two contiguous all-carbon quaternary stereocenters, a challenging structural feature in organic synthesis.[4] The intermediacy of labile β-hydroxy ketone **B** (R = H), prone to elimination and retro-aldol reactions, greatly limits the choice of reagents and renders mimicking this late-stage aldol transformation a synthetically exigent challenge. The chemical synthesis of periconianone A (**1**) thus fits into the context of our research program on unusual biogenetic proposals for natural product synthesis.[5] In addition to its striking structural features, periconianone A (**1**) displays diverse biological activity.[3,6]

Another challenge besides the key aldol transformation in our synthetic plan is the stereoselective elaboration of the C7 carbinol unit. Although present in diverse bioactive eremophilane-type natural products, there has so far been no synthetic strategy addressing the construction of this structural motif. We approached this synthetic challenge and report herein on the first enantioselective total synthesis of periconianone A (**1**) applying an efficient crotyl-O-insertion and formal [2,3]-Wittig rearrangement sequence (**C** → **D**).[7]

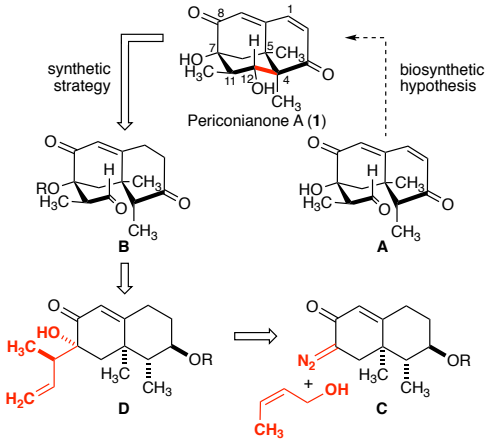
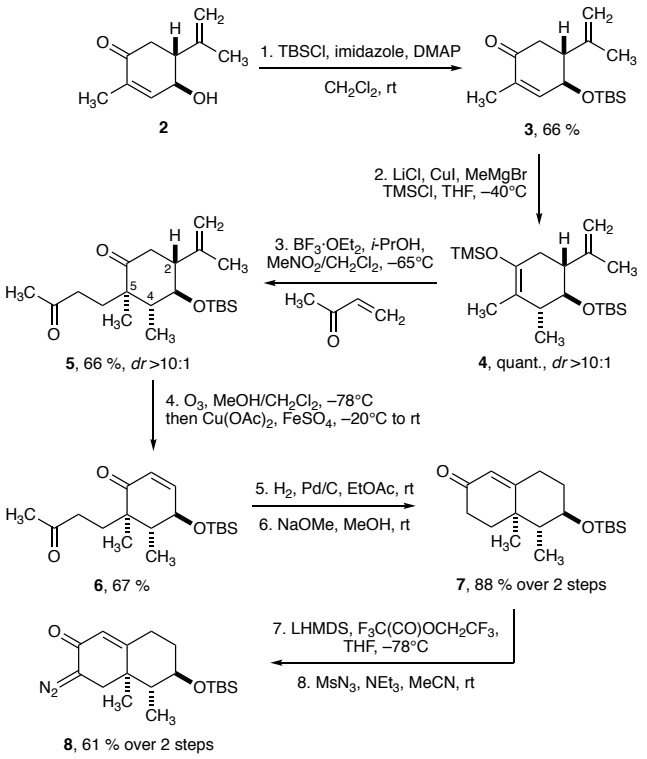


Figure 1. Synthetic strategy to periconianone A (**1**) inspired by a biogenetic hypothesis.

The synthesis starts from known γ-hydroxy carvone (**2**, prepared from (*R*)-carvone in two steps),[8] which was protected with TBSCl to give silyl ether **3**. Conjugate addition of methyl cuprate to enone **3** and trapping of the resulting enolate was conducted at –40°C to give access to TMS enol ether **4** with good diastereoselectivity (*dr* >10:1) and quantitative yield.[9] No conversion of the starting material was observed at lower reaction temperatures, whereas higher temperatures led to increased formation of the undesired diastereoisomer. Lewis acid-catalyzed Michael addition of TMS enol ether **4** to methyl vinyl ketone in the presence of $BF_3{\cdot}OEt_2$[10] gave the desired diketone **5** in 66 % yield, together with desilylated starting material, which was recycled. The isopropenyl group at C2 had by now served its role to establish the stereogenic centers at C4 and C5 and was therefore cleaved by Criegee fragmentation:[11] ozonolysis of the terminal double bond in **5** and subsequent treatment of the formed peroxy acetal intermediate with $Cu(OAc)_2$ and $FeSO_4$ triggered the fragmentation to yield enone **6**. Attempts to remove the isopropenyl group

later on after formation of the bicyclic structure, as well as treatment of the peroxy acetal intermediate with other reagents reported in the literature (Ac_2O, DMAP, Et_3N)[12] mainly led to cleavage of the terminal C=C double bond to form the acetyl group at C2. Cyclization of **6** under basic conditions yielded mixtures of the desired aldol product and an undesired Michael addition by-product, which prompted us to hydrogenate the reactive olefin using Pd/C as a catalyst. In fact, selective formation of the desired aldol product was achieved by enamine catalysis (pyrrolidine, AcOH), but due to its high reactivity, the formed dienone moiety proved to be unsuitable for the ensuing steps of the synthesis. Octalone **7** was isolated as a crystalline solid in 88 % yield over two steps after treatment of the diketo intermediate with NaOMe in MeOH (Scheme 1).

Scheme 1. Synthesis of diazoketone 8.



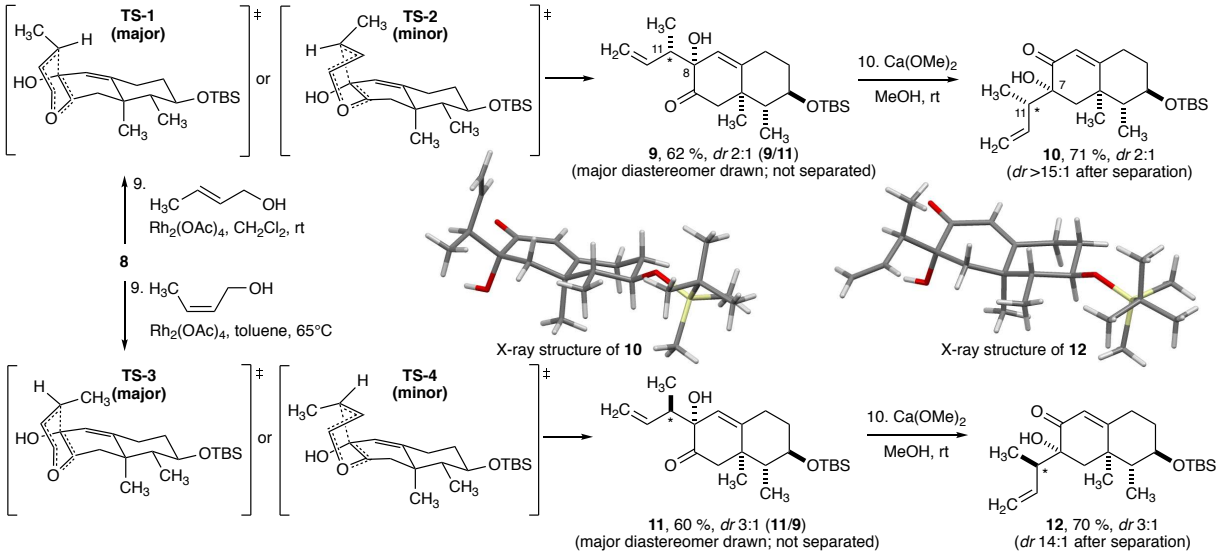
With this short and efficient route for the preparation of ample quantities of octalone **7** in hand, the stage was set to investigate the key O-H insertion/formal [2,3]-sigmatropic rearrangement sequence for installing, after oxidative cleavage, the three carbon-fragment to complete the C_{15} skeleton. The required precursor featuring a diazo group at C7 was prepared by a two-step protocol,[13] as direct diazoketone formation under basic conditions had proven unsuccessful. Trifluoroacylation was performed quantitatively by treatment of the enolate of **7** with trifluoroethyl trifluoroacetate. The trifluoroacylated compound was then treated with mesyl azide and triethylamine to yield diazoketone **8** in 61 % yield over two steps.

In the presence of $Rh_2(OAc)_4$, diazoketone **8** reacted with *trans*-crotyl alcohol in a Rh-catalyzed insertion of the carbenoid into the O-H bond to furnish α-allylated α-hydroxyketone **9** in 62 % yield and with a diastereomeric ratio of 2:1 (Scheme 2). Initially, we had anticipated isolation of the ether as the primary insertion product, which would have been amenable to a [2,3]-Wittig rearrangement upon treatment with base to form the desired α-hydroxyenone **10**.[14] There are hardly any literature precedents for reactions of α-diazoketones with allylic alcohols in the presence of Rh(II) to form the corresponding α-alkylated α-hydroxyketones,[15] and application in total synthesis has only been reported by Wood and co-workers.[16] Mechanistic studies revealed that the (*Z*)-enol intermediates formed upon O-H insertion of the carbenoid may subsequently undergo a [3,3]-sigmatropic rearrangement instead of ketonization to the α-keto ether, and that this fast Claisen rearrangement is not catalyzed by Rh.[15] Our observations are in line with these reports, as the α-keto ether, formed as side product during the course of the reaction, did not undergo a [3,3]-rearrangement, even after prolonged reaction time. Neither did heating of the isolated α-keto ether in the absence or presence of $Rh_2(OAc)_4$ lead to the formation of any significant amounts of the expected [3,3]-rearranged product **9**. Furthermore, we were surprised by the moderate diastereoselectivity of 2:1 at C11 in the rearranged carbinol **9**, as the employed *trans*-crotyl alcohol contained only 5 % of the *cis*-isomer and we had anticipated the reaction to proceed *via* a concerted sigmatropic and therefore stereospecific process. A possible explanation for this observation can be found in a report by Ireland and co-workers, who investigated the preference of chair- and boat-like transition-state geometries in the ester enolate Claisen rearrangement.[17] Based on Ireland's observations, we suppose that the usually disfavored twist-boat transition-state (**TS-2**, Scheme 2) might be accessible in this [3,3]-rearrangement, thus enabling the formation of both diastereoisomers, which could not be separated by column chromatography.

With the α-ketocarbinol **9** at hand, we investigated the [1,2]-allyl shift from C8 to C7 through an α-ketol rearrangement. This reaction, also referred to as an acyloin rearrangement, is a well-established transformation and its synthetic application has been considerably expanded since applied in the D-ring homoannulation of steroids.[18] Nevertheless, its application in total synthesis is rare[18a,19] and most often unanticipated.[16b,20] The α-ketol rearrangement is a reversible process and its driving force is formation of the more stable α-hydroxy carbonyl isomer. Literature examples most often involve release of ring strain[18] or formation of a more stable β-dicarbonyl compound starting from β-hydroxy α-diketones.[16a,d] By comparing the thermodynamic properties of **9** and **10**, we hypothesize the driving force to be formation of the conjugated enone moiety in **10**, a mechanistic possibility not previously suggested for this type of rearrangement. After extensive screening of various inorganic bases, Lewis and Brønsted acids,[21] the best results were obtained for the reaction of **9/11** (2:1) mediated by $Ca(OMe)_2$ in MeOH at room temperature to give access to the α-allylated α-hydroxyenone **10** in 71 % yield and with fully retained configuration at stereocenters C7 and C11. Besides basic or Lewis acidic conditions, various metal salts are known to promote α-ketol rearrangements.[18a] However, to the best of our knowledge, this is the first example for an α-ketol rearrange-

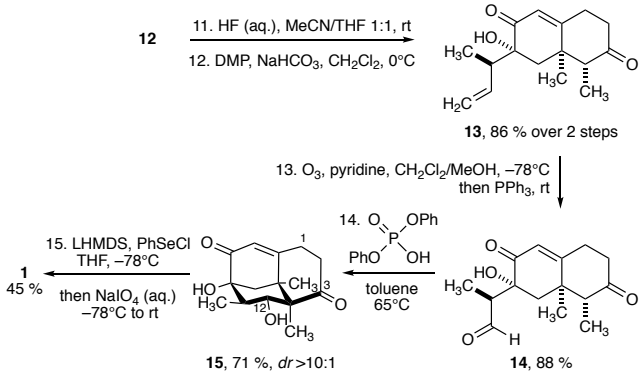
ment by a simple and cost-efficient calcium salt. The structure of **10** was confirmed by single-crystal X-ray analysis,[22] which revealed that the undesired diastereoisomer with *S*-configuration at C11 was formed preferentially in the Claisen rearrangement. We were delighted to find that with *cis*-crotyl alcohol, the insertion/[3,3]-sigmatropic rearrangement process gave a diastereomeric product mixture of 3:1 in favor of the desired isomer **11** with *R*-configuration at C11. This process did not take place at room temperature and the mixture of crotyl alcohol and $Rh_2(OAc)_4$ had to be heated to 65°C in toluene or 1,2-dichloroethane, before diazoketone **9** was slowly added. Treatment of α-ketocarbinol **11** with $Ca(OMe)_2$ gave access to the desired α-allylated hydroxyenone **12** in 70 % yield and, after separation, with a diastereomeric ratio of 14:1 in favor of the desired isomer, whose structure was confirmed by single-crystal X-ray analysis.[22]

Scheme 2. Sequence of Rh-mediated O-H insertion, [3,3]-sigmatropic rearrangement and α-ketol rearrangement for the installation of the tertiary alcohol at C7.



The endgame involved cleavage of the TBS group of α-hydroxyenone **12** and oxidation of the resulting secondary OH group by Dess-Martin periodinane (DMP) to afford the carbonyl group at C3 (Scheme 3). Ozonolysis of the terminal double bond in diketone **13** set the stage for the key aldol addition of aldehyde **14**.

Scheme 3. Construction of the 6/6/6 tricarbocyclic framework.



Various basic and acidic conditions only induced a retro-aldol reaction by cleavage of propanal to form the undesired diosphenol. After extensive screening, organic phosphonic acids,[23] very rarely applied for aldol reactions, were shown to mediate the desired aldol addition without significant side product formation, even in the presence of the free tertiary alcohol at C7. Treatment of aldehyde **14** with diphenyl phosphate in toluene at 65°C gave tricycle **15** in 71 % yield and full diastereoselectivity. Final oxidation of the C1–C2 bond was achieved by selenoxide elimination. α-Selenylation using LHMDS and phenylselenyl chloride was followed by oxidation with $NaIO_4$[24] to give periconianone A (**1**) in 45 % yield. The spectroscopic data of the synthetic sample matched those reported for the natural product.[3]

In this communication, we report on the first total synthesis of periconianone A with a late-stage cyclization event as one of the key steps. The biomimetic aldol reaction takes place without the need of a protecting group for the tertiary alcohol, and in total only one protecting group had to be employed to achieve this total synthesis. Additional distinctive features of our approach involve a Criegee fragmentation to remove the chiral anchor, as well as a Rh-mediated O-H insertion followed by a spontaneous Claisen reaction and an α-ketol rearrangement. In particular, this rearrangement sequence allowed for the stereoselective installation of the C7 carbinol, a problem which has not yet been addressed in synthetic endeavors aimed at the preparation of eremophilane-type natural products. This strategy allows for the concise preparation of other eremophilane-type natural products bearing this C7 structural motif and will provide access to derivatives of periconianone A (**1**) for SAR studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, analytical data, spectra (^{1}H and ^{13}C NMR) for all new compounds (PDF)
Crystallographic data for **10** and **12** (CIF)

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Notes

The authors declare no competing financial interest.

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(21) Screening conditions are summarized in a table given in the supporting information.

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